Supporting Statement

Reporting Requirements

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients

A. Justification

1. Circumstances Necessitating Information Collection

The Food and Drug Administration (FDA) is requiring pediatric studies of certain new drugs and biological products to ensure that those products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval.

Many new drugs and biological products represent treatments that are the best available treatment for children, but most of them have not been adequately tested in the pediatric population. As a result, product labeling frequently fails to provide directions for safe and effective use in pediatric patients. This rule is intended to increase the number of new drugs and biological products, with clinically significant use in children, that carry adequate labeling for use in that subpopulation.

The circumstances that the rule and information collection are intended to address are: (1) Avoidable adverse drug reactions in children -- drug reactions that occur because of the use of inadvertent drug overdoses or other drug administration problems that could have been avoided with better information on appropriate pediatric use; and (2) undertreatment of children with a potentially safe and effective drug because the physician either prescribed an inadequate dosage or regimen, prescribed a less effective drug, or did not prescribe a drug, due to the physician's uncertainty about whether the drug or the dose was safe and effective in children.

OMB approval is requested for the following reporting requirements:

21 CFR 201.23	Application holders may be required to submit a supplement containing data adequate to assess whether the drug product is safe and effective in pediatric populations.

21 CFR 312.47(b)(1)(iv)	Sponsors should submit background information on the sponsor's plan for Phase 3, including plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies.
21 CFR 312.47(b)(2)	Sponsors should submit to FDA information on the status of needed or ongoing pediatric studies.
21 CFR 314.50(d)(7)	Applicants must submit a pediatric use section, describing any investigations of the drug for use in pediatric populations.
21 CFR 314.55(a)	Applications must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in pediatric subpopulations, and to support dosing and administration information.
21 CFR 314.55(b)	Applicants may request a deferred submission of some or all assessments of safety and effectiveness required under (a).
21 CFR 314.55(c)	Applicants may request a full or partial waiver of the requirements under (a).
21 CFR 314.81(b)(2)(i)	Applicant's annual report must include a brief summary of whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric

	population have been initiated.
21 CFR 314.81(b)(2)(vi)(c)	Applicant's annual report must include an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information.
21 CFR 314.81(b)(2)(vii)	Applicant's annual report must include a statement whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies.
21 CFR 601.27(a)	Applications for new biological products must contain data that are adequate to assess the safety and effectiveness of the biological product for the claimed indications in pediatric subpopulations, and to support dosing and administration information.
21 CFR 601.27(b)	Applicants may request a deferred submission of some or all assessments of safety and effectiveness required under (a).
21 CFR 601.27(c)	Applicants may request a full or partial waiver of the requirements under (a).
21 CFR 601.37(a)	Sponsors must submit to FDA a brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to

	support appropriate labeling for the pediatric population have been initiated.
21 CFR 601.37(b)	Sponsors must submit to FDA an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information.
21 CFR 601.37(c)	Sponsors must submit to FDA a statement on the current status of any postmarketing studies in the pediatric population performed by, on or behalf of, the applicant.

2. How, By Whom, and for What Purpose

FDA is requiring pediatric studies of certain new drugs and biological products to ensure that those products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval.

The final rule includes the following reporting requirements: (1) Reports on planned pediatric studies in INDs; (2) Reports for end-of-phase 1 and end-of-phase 2 meetings and reports for pre-NDA meetings; (3) Summaries of data on pediatric safety and effectiveness in NDAs; (4) Reports assessing the safety and effectiveness of certain drugs and biological products for pediatric use in NDAs and BLAs or in supplemental applications; (5) Requests seeking deferral of required pediatric studies; (6) Requests seeking waiver of required pediatric studies; (7) Postmarketing reports of analyses of data on pediatric safety and effectiveness; (8) Postmarketing reports on patient exposure to certain marketed drug products; (9) Postmarketing reports on labeling changes initiated in response to new pediatric data; and (10) Postmarketing reports on the status of required postapproval studies in pediatric patients.

The purpose of these reporting requirements is to address the lack of adequate pediatric labeling of drugs and biological

products by requiring the submission of evidence on pediatric safety and effectiveness for products with clinically significant use in children.

3. Considerations of Information Technology

Reports required under this final rule are for drugs that are the subjects of planned, pending, or approved marketing applications. The following is a summary of FDA's efforts to receive electronically marketing applications and related submissions.

In the mid-1980's, FDA began working with pharmaceutical sponsors to develop Computer-Assisted New Drug Applications (CANDA). CANDAs were designed to provide information (text, data, image) electronically to facilitate the review of applications. These efforts yielded valuable information but were limited because for each new drug review division sponsors tended to develop different hardware and software approaches. A reviewer might be confronted with an array of hardware, software, and review tools to conduct a review that differed between sponsors and applications. Also, CANDAs were never approved as a substitute for the archival copy, so firms were still required to submit copies.

One solution to limitations of CANDAs was an approach whereby staff responsible for a particular review discipline (eg, chemistry, clinical) worked directly with pharmaceutical sponsors to develop a consistent approach that would be applicable to all sponsors and to all review divisions. Focus on this approach has evolved into the Electronic Regulatory Submission and Review (ERSR) Program. This new initiative is intended to ensure both the electronic availability of information and the means to manipulate this information electronically to yield a review.

ERSR has been made possible by other developments. The harmonization of FDA Form 356h has ensured that NDAs, ANDAs, and Biological License Applications would contain comparable information in the same sections of the submission. The promulgation of the "Electronic Records; Electronic Signatures" final rule allowed FDA to accept electronic submissions without an accompanying paper archival copy because electronic records are equivalent to paper records and electronic signatures are equivalent to hand-written signatures provided the requirements of 21 CFR Part 11 are met and the document has been identified in the agency's public docket as being acceptable for filing. The Guidance for Industry on "Archiving Submissions in Electronic Format - NDAs" provides for the receipt and archival of electronic report forms and tabulations. Another Guidance for Industry entitled "Providing Regulatory Submissions in Electronic

Format - NDAs" is currently under development.

ERSR is made up of a variety of projects that are in different stages of development and implementation. These projects are categorized into 3 areas: First, "Electronic Submissions" includes standards-related projects to define the format and content of regulatory submissions; written guidance for industry to follow in preparing electronic submissions; an Electronic Document Room project to accommodate the receipt, archive, and storage of electronic transmissions; an Electronic Gateway project to provide an agency-level central point for receipt of secure electronic transmissions and routing to the Centers; and scientific databases that include structured databases, reference guides, and analytical tools used by reviewers. Second, "Corporate Databases, Documentbases and Applications" includes projects under the Electronic Document Management System and the Management Information System. Third, other electronic initiatives including technical infrastructure, technical support, and training.

ERSR will impact the underlying business processes related to regulatory submissions and reviews. Document rooms will handle electronic media rather than paper copies. Reviewers will review submissions online and generate their review documents online. Reviewers will conduct data analysis using structured databases, which combine data extracted from the submission under review as well as historical data from earlier submissions. Industry sponsors and manufacturers will experience reduced paper costs and manpower to compile paper submissions and better access to application status information through electronic mail.

4. Identification of Duplication

The reporting required as a result of this rule is not currently required by FDA and would not duplicate any other information collection. This reporting is the only practical means available to FDA to ensure that new drugs and biological products with clinically significant use in children carry adequate labeling for use in that subpopulation.

5. Small Businesses

As explained in the "Analysis of Impacts" section of the final rule, FDA has concluded that the rule does not have a significant economic impact on a substantial number of small entities.

6. Consequences of Less Frequent Information Collection

FDA would be unable to ensure that new drugs and biological products with clinically significant use in children carry adequate labeling for use in that subpopulation.

7. Inconsistencies with 5 CFR 1320.60

Data collection for applications is consistent with all the requirements of section 1320.6.

8. Consultations with Outside Sources

In the Federal Register of October 16, 1992, FDA proposed to revise the "Pediatric Use" subsection of the prescription drug labeling regulations to allow a broader basis for the inclusion of information about use of a drug in the pediatric population. The proposal, which was finalized in the Federal Register of December 13, 1994, allowed pediatric claims based not only on adequate and well-controlled studies in the pediatric population but also, in some cases, on such trials in adults. The regulation described other data needed when pediatric claims are based on trials in adults, and indicated specific labeling language and the location of various kinds of information. FDA issued this rulemaking because most prescription drugs lack adequate information about their use in pediatric populations and, thus, practitioners are reluctant to prescribe certain drugs for pediatric patients or may prescribe them inappropriately, choosing dosages that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. FDA received comments on the proposed rule from prescription drug manufacturers, prescribers, professional societies, organizations with special interests in the pediatric population, and the lay public.

FDA proposed the requirements that are the subject of this final rule in the Federal Register of August 15, 1997, because, as explained in the preamble to the proposal, there had not been a substantial increase in the number of drugs and biological products for which there is adequate pediatric use information. FDA received 54 written comments on the proposed rule from pediatricians, professional societies, parents, members of the pharmaceutical industry, organizations devoted to specific diseases, and patient groups. FDA also held a day-long public hearing on October 27, 1997, at which recognized experts in the field, members of the pharmaceutical industry, and other interested parties were given an opportunity to discuss the

issues raised by the proposed rule. All of these comments, as well as FDA's responses, are discussed in the "Comments on the Proposed Rule" section of the final rule.

9. Payments or gifts to Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under these requirements.

10. Confidentiality of Information

Confidentiality of the information submitted under these reporting requirements is protected under 21 CFR 314.430 and 601.51.

11. Sensitive Questions

There are no questions of a sensitive nature.

12. Total Hour Burden to Respondents

Estimated Annual Reporting Burden					
CFR Section	No. of Respon-dents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
201.23	2	1	2	48	96
312.47(b)(1)(iv)	27	1.2	32	16	512
312.47(b)(2)	36	1.3	46	16	736
314.50 (d)(7)	213	1	213	50	10,650
314.55(a)	51	1	51	48	2,448
314.55(b)	51	1	51	24	1,224
314.55(c)	176	1	176	8	1,408

314.81 (b)(2)(i)	625	1	625	8	5,000
314.81 (b)(2) (vi)(c)	625	1	625	24	15,000
314.81 (b)(2) (vii)	625	1	625	1.5	937.5
601.27(a)	2	1	3	48	144
601.27(b)	2	1	3	24	72
601.27(c)	3	1	4	8	32
601.37(a)	69	1	69	8	552
601.37(b)	69	1	69	24	1,656
601.37(c)	69	1	69	1.5	103.5
Total					40,571

13. Total Annual Cost Burden to Respondents

The cost for submitting the application sections, supplements, and requests required under the final rule is based on the following wage rates: Upper management at $70.00 per hour; middle management at $35.00 per hour; and clerical assistance at $23.00 per hour. Using an averaged wage rate of $50.00 per hour (based on the percentage of time required for each type of employee), the total cost burden to respondents would be **$1,996,650.00** (39,933 x $50).

14. Annualized Cost to FDA

FDA estimates that it would take application reviewers an average of approximately 50 hours to review each additional application section, supplement, and request required under 21 CFR 201.23, 312.47(b)(1)(iv), 312.47(b)(2), 314.50(d)(7), 314.55(a), 314.55(b), 314.55(c), and 601.27(a), (b), and (c), and an average of approximately 4 hours to review each additional annual report

section required under 21 CFR 314.81(b)(2)(i), (b)(2)(vi)(c), and (b)(2)(vii), and 21 CFR 601.37(a), (b), and (c). Based on an average hourly cost of $55.00 per hour for this level of reviewer (including overhead expenses and support), the total cost to FDA would be **$2,086,040.00** (592 submissions x 50 hours x $55 = $1,628,000.00; 2082 submissions x 4 hours x $55 = $458,040.00).

15. Publication of Information Collection Results

FDA does not intend to publish tabulated results of the information collection requirements that would be imposed by these regulations.

17. Display of OMB Approval Date

There are no forms associated with this collection.

18. Exceptions to the Certification Statement - Item 19

There are no exceptions to the "Certification for Paperwork Reduction Act Submissions" for this rule. This rule complies with 5 CFR 1320.9.

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement identified in Item 19, " Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.

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